Comparison of ondansetron with ondansetron and dexamethasone in prevention of PONV in diagnostic laparoscopy

V. Rajeeva MD,
N. Bhardwaj MD,
Y.K. Batra MD MNAMS,
L.K. Dhaliwal MS*

Purpose: To compare the efficacy of ondansetron-dexamethasone combination with ondansetron alone for prevention of postoperative nausea and vomiting (PONV).

Methods: This double blind, randomized study was carried out in 51 female patients, aged 20-40 yr, ASA-1 physical status undergoing gynecological diagnostic laparoscopy. Group I (n = 26) received 4mg ondansetron *iv* and group 2 (n = 25) received a combination of 4 mg ondansetron and 8 mg dexamethasone *iv* soon after induction of anesthesia. Postoperatively patients were assessed hourly for four hours and then at 24 hr for nausea, vomiting, pain and post anesthetic discharge score. Vomiting occurring up to two hours was considered early vomiting and from 2-24 hr as delayed vomiting.

Results: The postoperative nausea score was lower in patients receiving a combination of ondansetron and dexamethasone (3.76) than ondansetron alone (4.38) at 0 hr ($P < 0.01$), 2 hr ($P < 0.05$) and 24 hr ($P < 0.01$). In group 1, 38.5% of patients had a nausea score of ≥ 5 (major nausea) compared with only 12% of patients in group 2 ($P < 0.025$). The overall incidence of vomiting was greater in group I (35%) than in group 2 (8%) ($P < 0.05$). The combination group showed better control of delayed vomiting compared with the ondansetron group (4% *vs* 35%) ($P < 0.01$).

Conclusion: The combination of ondansetron and dexamethasone provides adequate control of PONV, with delayed PONV being better controlled than early PONV.

Objectif : Comparer l'efficacité d'une combinaison d'ondansétron et de dexaméthasone avec l'ondansétron employé seul pour la prévention de nausées et de vomissements postopératoires (NVPO).

Méthode : La présente étude, randomisée et en double aveugle, a été réalisée auprès de 51 patientes, âgées de 20 à 40 ans, d'état physique ASA I qui devaient subir une laparoscopie gynécologique. Le groupe I (n = 26) a reçu 4mg d'ondansétron *iv* et le groupe 2 (n = 25), une combinaison de 4 mg d'ondansétron et de 8 mg de dexaméthasone *iv* peu après l'induction de l'anesthésie. À la suite de l'intervention, on a évalué les nausées, les vomissements, l'échelle de douleur et de congé à chaque heure, pendant quatre heures, et à 24 h. Les vomissements se produisant jusqu'à deux heures après l'intervention étaient considérés comme des vomissements précoces et ceux qui survenaient entre 2 et 24 h, comme des vomissements tardifs.

Résultats : Le score des nausées postopératoires était plus bas chez les patientes qui avaient reçu une combinaison d'ondansétron et de dexaméthasone (3,76) plutôt que de l'ondansétron seulement (4,38) à 0 h ($P < 0,01$), à 2 h ($P < 0,05$) et à 24 h ($P < 0,01$). Dans le groupe 1, 38,5 % des patientes ont présenté un score de nausées 5 (nausées importantes) comparativement à 12 % seulement des patientes dans le groupe 2 ($P < 0,025$). L'incidence totale de vomissements était plus grande dans le groupe I (35 %) que dans le groupe 2 (8 %) ($P < 0,05$). Le groupe ayant reçu une combinaison de médicaments, comparé au groupe qui a reçu de l'ondansétron, a présenté un meilleur contrôle des vomissements tardifs (4 % *vs* 35 %) ($P < 0,01$).

Conclusion : La combinaison d'ondansétron et de dexaméthasone fournit un bon contrôle des NVPO, meilleur pour les NVPO précoces que pour les NVPO tardifs.

From the Departments of Anaesthesia and Obstetrics and Gynaecology,* Post Graduate Institute of Medical Education and Research, Chandigarh.

Address correspondence to: Dr. Neerja Bhardwaj, Flat No. 124-C, Sector 24-A, Chandigarh, India. Tel: 91-172- 541031; Fax: 91-172-540401

Accepted for publication October 3, 1998

NAUSEA and vomiting is a common and distressing postoperative complication with an incidence of 25-43% after both inpatient and day care surgery.[1] After gynecological laparoscopy, a commonly performed day care procedure the incidence is 50-80%.[2] PONV is multifactorial in origin, therefore none of the available antiemetics is entirely effective in all patients. The use of a combination of antiemetic drugs could be a more effective alternative. After encouraging results obtained in preventing cisplatin chemotherapy induced vomiting,[3-4] an ondansetron- dexamethasone combination has been used for PONV after major gynecological surgery with good results.[5,6] This combination has not been tried after gynecological laparoscopy, a procedure with a high incidence of PONV. The present study was designed to assess the efficacy of ondansetron-dexamethasone combination for prevention of PONV in gynecological day care surgeries.

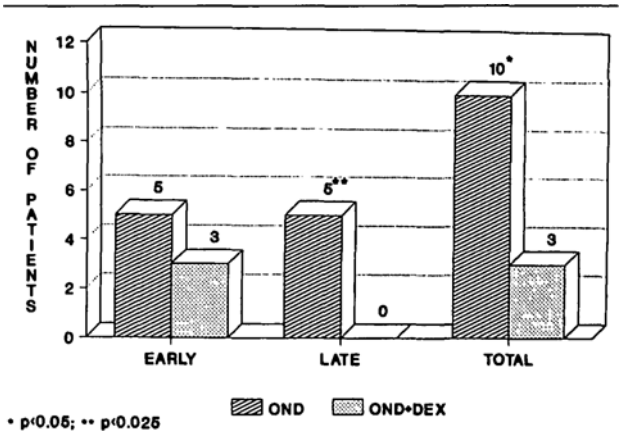

FIGURE 1 The incidence of major nausea in the two groups. The incidence of major nausea was less in the combination group in the late postoperative period ($P < 0.025$).

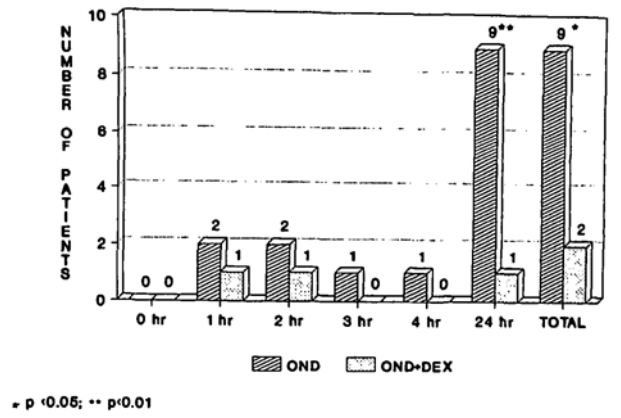

FIGURE 2 The incidence of emesis at various time intervals. The difference was signifincant at 24 hr ($P < 0.01$) showing that the combination caused better control of delayed PONV.

Material and methods

In this prospective, randomized, double blind investigation we studied 51 ASA I female patients, aged 20-40 yr, undergoing elective diagnostic laparoscopy under general anesthesia. Informed written consent and local ethics committee approval was obtained before commencing the study. The patients were randomly divided by random number chart into two groups: 26 patients received 4 mg ondansetron diluted in 5 ml (group 1) and the remaining 25 patients received 4 mg ondansetron plus 8 mg dexamethasone diluted to 5 ml (group 2). The study drugs were given intravenously (*iv*) soon after tracheal intubation.

Patients who were obese (BW 20% more than expected for their age), pregnant, or had a history of motion sickness or PONV were excluded from the study. Patients who had received antiemetics within 24 hr of surgery, patients needing chronic steroid therapy, those suffering from diabetes mellitus, intestinal obstruction or hiatus hernia were not included.

The patients were premedicated with 10 mg diazepam *po* on the night before surgery and 5 mg on the morning of the surgery. Anesthesia was induced with 5 $mg \cdot kg^{-1}$ thiopental and tracheal intubation was facilitated with 5 $mg \cdot kg^{-1}$ succinylcholine *iv*. Intermittent positive pressure ventilation was performed using low airway pressures to avoid gastric distension. The test drug was given soon after tracheal intubation. Anesthesia was maintained with nitrous oxide in oxygen (F_IO_2 0.33), 0.08 $mg \cdot kg^{-1}$ vecuronium and 1 $mg \cdot kg^{-1}$ meperidine *iv*. Ventilation was controlled utilizing a flow of 100 $ml \cdot kg^{-1}$ and a respiratory rate of 12 bpm using a Bain anesthetic circuit. Intraoperative oral and pharyngeal suctioning were avoided. The muscle paralysis was reversed at the end of surgery with 0.05 $mg \cdot kg^{-1}$ neostigmine and 0.01 $mg \cdot kg^{-1}$ glycopyrrolate *iv*. Diclofenac 75 mg *im* was given before the reversal of neuromuscular blockade for postoperative pain. Intraoperative monitoring included heart rate, noninvasive blood pressure, $P_{ET}CO_2$, oxygen saturation and ECG. Patients were monitored for nausea, vomiting, pain, vital signs and post anesthetic discharge score. All patients were monitored every hour for four hours, or until they achieved the discharge criteria and then interviewed after 24 hr.

Nausea was measured using an 11 point numerical visual analogue scale with 0 = no nausea and 10 = nau-

TABLE I Patient characteristics (Mean ± SD)

	Group 1 (n = 26)	*Group 2 (n = 25)*
Age (yr)	28.85 ± 5.29	28.72 ± 4.46
Weight (kg)	48.88 ± 6.38	50.84 ± 6.92
LMP (days)	6.42 ± 1.33	6.48 ± 1.45
Duration of procedure (min)	28.54 ± 4.45	29.00 ± 3.61
Duration of insufflation (min)	13.12 ± 3.40	12.76 ± 2.07

P-NS

TABLE II Postoperative nausea score (mean ± SD)

Time	*Group 1*	*Group 2*
0 hr	1.08 ± 1.55	0.16 ± 0.55†
1 hr	2.65 ± 1.77	1.88 ± 1.62
2 hr	3.54 ± 1.86	2.92 ± 1.22*
3 hr	3.15 ± 1.05	3.16 ± 1.03
4 hr	2.65 ± 0.94	2.56 ± 1.04
4-24 hr	3.81 ± 0.69	2.64 ± 1.29†

* $P < 0.05$; † $P < 0.01$

TABLE III Severity of nausea : Number (Percentage)

Type	*Early*		*Late*	
	Group 1	*Group 2*	*Group 1*	*Group 2*
Nil	0	1 (4%)	0	1 (4%)
Mild	21 (81%)	21 (84%)	21 (81%)	24 (96%)
Moderate	5 (19%)	3 (12%)	4 (15%)	0
Severe	0	0	1 (4%)	0
Total (nausea)	26 (100%)	24 (96%)	26 (100%)	24 (96%)

TABLE IV Severity of emesis : Number (Percentage)

Type	Early		Late	
	Group 1	Group 2	Group 1	Group 2
Nil	22 (85%)	23 (92%)	17 (65%)	24 (96%)*
Mild	4 (15%)	2 (8%)	7 (28%)	1 (4%)
Moderate	0	0	2 (8%)	0
Severe	0	0	0	0
Total (emesis)	4 (15%)	2 (8%)	9 (35%)	1 (4%)*

* $P < 0.01$

TABLE V Patients discharge times - number (percentage)

Time	Group 1	Group 2
0 hr	0	0
1 hr	3 (12%)	3 (12%)
2 hr	19 (73%)	18 (72%)
3 hr	3 (12%)	4 (16%)
4 hr	0	0
> 4hr	1 (4%)	0

sea as bad as can be. A score of > 5 was considered severe, 5 = moderate and < 5 = minimal. The moderate and severe nausea was considered as major nausea. During the period of monitoring the vomiting episodes of > 2 were considered severe, 2 as moderate and < 2 as mild. Rescue antiemetic consisted of 0.15 $mg \cdot kg^{-1}$ metoclopramide *iv* and was given for more than two episodes of vomiting. Vomiting occurring up to two hours was taken as early vomiting whereas delayed vomiting consisted of vomiting over 2-24 hr.

Pain was measured on an 11 point numerical visual analogue scale similar to that for nausea. Rescue analgesia (75 mg diclofenac *im*) was given when the pain score was > 5. For discharge postanesthetic discharge scoring system described by Chung *et al.*[7] was utilized.

Nausea, pain, discharge score and patient characteristics were compared using student t test. Incidence of nausea, vomiting, delayed recovery, side effects and number of patients needing rescue antiemetic were compared using chi square test.

Results

The two groups were comparable regarding age, weight, last menstrual period (LMP), duration of procedure, and duration of insufflation (Table I). The postoperative nausea score was numerically lower in patients who had received a combination of ondansetron and dexamethasone than ondansetron alone at all times until 24 hr and the difference was statistically significant at 0, 2 and 24 hr (Table II). The mean maximum nausea score was greater in group 1 (4.38) than in group 2 (3.76). In group 1 38.5% of patients had a nausea score of ≥ 5 (major nausea) compared with 12% in group 2 ($P < 0.05$; Figure 1). There was no difference in mild, moderate or severe nausea during the early and late postoperative period in both the groups (Table III).

The overall incidence of vomiting was greater in group 1 (35%) than in group 2 (8%, $P < 0.05$). Analysis of results at various time intervals showed that there was no difference in emesis between the two groups except at 24 hr when only one patient (4%) in group 2 vomited compared with nine (35%) in group 1 (Figure 2) There was no difference in the incidence of early vomiting or its severity between the two groups (Table IV). In the late postoperative period the incidence of vomiting was less in group 2 (4%) than in group 1 (35%; Table III). There was no difference in the mild, moderate and severe vomiting in the late postoperative period.

The pain scores in the two groups at all times did not show any difference and the need for rescue anal-

gesia did not differ. The average time to attain discharge criteria was 2.11 ± 0.76 hr in group 1 and 2.08 ± 0.49 in group 2 (*P*:NS). One patient in group 1 needed > 4 hr to attain discharge criteria compared with none in group 2 (Table V). The need for rescue antiemetics did not differ between the two groups.

Discussion

The combination of 4 mg ondansetron and 8 mg dexamethasone reduced the incidence of emetic episodes compared with ondansetron alone ($P < 0.05$). Although the combination therapy did not decrease the incidence of postoperative nausea, it reduced its severity and incidence of major nausea episodes. In addition, it caused better control of delayed nausea and vomiting rather than early PONV.

Postoperative nausea and vomiting is a common sequel of general anesthesia and a leading cause of delayed discharge and unanticipated hospital admissions after ambulatory surgery. Many factors have been thought to contribute to PONV[2] and we tried to control most of them. Patients with a low threshold for vomiting such as gastroparesis, motion sickness, previous PONV and obesity were excluded from the study. Procedures which involved touching the ovaries or fallopian tubes were also excluded.[8] Gastric distension, repeated suctioning and naso-gastric tube insertion were avoided during anesthesia.[9]

Ondansetron, a selective $5HT_3$ receptor antagonist has been shown to be effective in the prevention and treatment of PONV in day care gynecological laparoscopy when used in a dose of 4 mg *iv*.[10-12] Since none of the available antiemetics, including ondansetron, is entirely effective in all patients, the concept of combination therapy was introduced by Parikh[13] in chemotherapy induced vomiting. Although the role of steroids as antiemetics was established in 1980[14] dexamethasone was introduced later. The mechanism of action of corticosteroids is unknown but may be related to inhibition of prostaglandin synthesis,[15] decrease in 5HT levels in the central nervous system[16] or by an anti-inflammatory action at the operative sites.[5]

The combination of ondansetron and dexamethasone has been tried to prevent PONV after major gynecological surgery with success but no study has compared the effectiveness of this combination in day care surgery. Several drugs have been tried to control nausea, of which ondansetron has been shown to be the best by several authors.[10,12] In all these studies the incidence of nausea has been very variable, probably related to ethnic variations, different anesthetics and the different type and duration of surgery. In our study all patients of both the groups demonstrated nausea, which was of a mild nature with no difference between early and late nausea. McKenzie *et al.*[5] also noted lower postoperative nausea scores in the combination group as was seen in our study. Fewer patients in the combination group had major nausea (39% *vs* 12%) and the incidence of late major nausea was also decreased. These findings are similar to the results obtained by Lopez *et al.*[6] where only 12% of patients in the combination group had late nausea as compared with 38% in the ondansetron only group.

In our study, 35% of patients had vomiting after 4 mg ondansetron which is comparable to the results obtained by Mckenzie.[5] In a study by Lopez *et al.*[6] none of the patients had early emesis whereas 24% of patients had emesis at 24 hr after 4 mg ondansetron. In contrast 15% of patients had early emesis while 35% had delayed emesis in our study. This difference may be due to the different surgical procedure in which the study was conducted. The incidence of vomiting after combination therapy was 8% in our study which is comparable to the studies of McKenzie[5] and Lopez.[6] Delayed vomiting was better controlled (4%) after combination therapy than was the early emesis (8%). These results do not agree with those of Lopez *et al.* where no patient vomited in the first two hours after surgery but 4% had vomited by 24 hr. In their study patients were undergoing major gynecological surgery of a longer duration than in our study which may explain the different results. It is probable that the action of dexamethasone had not started by the time surgery was completed. This also explains the higher incidence of early vomiting in patients of our study. Corticosteroids interact with specific receptor proteins in target tissues to regulate the expression of corticosteroids - responsive genes, thereby changing the levels and array of proteins synthesized by the various target tissues. As a consequence of the time required for changes in gene expression and protein synthesis, most effects of corticosteroids are not immediate but become apparent after several hours.[17] This is of clinical importance because a delay generally is seen before beneficial effects of corticosteroid therapy becomes manifest. Recent studies have raised the possibility that some actions of corticosteroids are immediate and are mediated by membrane bound receptors.[18]

In conclusion, the present study showed that combination therapy reduced the incidence of major postoperative nausea and emesis but the early nausea and vomiting were no better controlled than with ondansetron alone. There was no improvement in the time taken to attain discharge criteria. Further studies are required to determine the optimum time for the

administration of this antiemetic combination for effective control of postoperative nausea and vomiting.

References

1 *Hirsh J.* Impact of postoperative nausea and vomiting in the surgical setting. Anaesthesia 1994; 49(Suppl): 30–3.

2 *Kenny GNC.* Risk factors for postoperative nausea and vomiting. Anaesthesia 1994; 49(Suppl): 6–10.

3 *Jones AL, Hill AS, Soukop M, et al.* Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. Lancet 1991; 338: 483–7.

4 *Smith DB, Newlands ES, Rustin GJS, et al.* Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin - containing chemotherapy. Lancet 1991; 338: 487–90.

5 *Mckenzie R, Tantisira B, Karambelkar DJ, Riley TJ, Abdelhady H.* Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. Anesth Analg 1994; 79: 961–4.

6 *López-Olaondo L, Carrascosa F, Pueyo FJ, Monedeso P, Busto N, Sáez A.* Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth 1996; 76: 835–40.

7 *Chung F.* Discharge criteria - a new trend. Can J Anaesth 1995; 42: 1056–8.

8 *Andrews PLR.* Physiology of nausea and vomiting Br J Anaesth 1992; 69(Suppl): 2S–19S.

9 *Watcha MF, White PF.* Postoperative nausea and vomiting. Its etiology, treatment and prevention. Anesthesiology 1992; 77: 162–84.

10 *Paxton LD, McKay AC, Mirakhur RK.* Prevention of nausea and vomiting after day care gynecological laparoscopy: a comparison of ondansetron, droperidol, metoclopramide and placebo. Anaesthesia 1995; 50: 403–6.

11 *Tang J, Watcha MF, White PF.* A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures Anesth Analg 1996; 83: 304–13.

12 *Raphael JH, Norton AC.* Antiemetic efficacy of prophylactic ondansetron in laparoscopic surgery: randomized, double-blind comparison with metoclopramide. Br J Anaesth 1993; 71: 845–8.

13 *Parikh PM, Charak BS, Banavali SD, et al.* A prospective randomized double-blind trial comparing metoclopramide alone with metoclopramide plus dexamethasone in preventing emesis induced by high-dose cisplatin. Cancer 1988; 66: 2263–4.

14 *Rich WM, Abdulhayoglu G, DiSaia PJ.* Methylprednisolone as an antiemetic during cancer chemotherapy -a pilot study. Gynecol Oncol 1980; 9: 193–8.

15 *Aapro MS, Plezia PM, Alberts DS, et al.* Double-blind crossover study of the antiemetic efficacy of high-dose dexamethasone versus high-dose metoclopramide. J Clin Oncol 1984; 2: 466–71.

16 *Young SN.* Mechanism of decline in rat brain 5-hydroxytryptamine after induction of liver tryptophan pyrrolase by hydrocortisone: roles of tryptophan catabolism and kynurenine synthesis. Br J Pharmacol 1981; 74: 695–700.

17 *Schimmer BP, Parker KL.* Adrenocorticotropic hormone - adrenocortical steroids and their synthetic analogs: inhibitors of the synthesis and actions of adrenocortical hormones. *In*: Goodman Gilman (Eds.). The Pharmacological Basis of Therapeutics, 9th ed. McGraw Hill 1996: 1459–85.

18 *Wehling M.* Novel aldosterone receptors: specificity conferring mechanism at the level of the cell membrane. Steroids 1994; 59: 160–3.